PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61M 5/32, 25/00

A1

(11) International Publication Number: WO 98/39042

(43) International Publication Date: 11 September 1998 (11.09.98)

(21) International Application Number: PCT/US97/04948

(22) International Filing Date: 25 March 1997 (25.03.97)

(30) Priority Data:
60/040,481 7 March 1997 (07.03.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/040,481 (CON)
Filed on 7 March 1997 (07.03.97)

(71)(72) Applicants and Inventors: JACKSON, Richard, R. [US/US]; One Atlantic Avenue, Swampscott, MA 01907 (US). WILLIAMS, John, N. [US/US]; 598 Barretts Mill Road, Concord, MA 01742 (US).

(74) Agent: WILLIAMS, John, N.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANESTHETIZING PLASTICS, DRUG DELIVERY PLASTICS, AND RELATED MEDICAL PRODUCTS, SYSTEMS AND METHODS

(57) Abstract

A compound with topical anesthetic properties is incorporated in polymeric material suitable for forming products useful in the medical arts. A hydrophobic anesthetic compound is used which is more soluble in the polymer than in water so that a quantity of anesthetic compound can be stored in solution in the polymer and not be washed out by aqueous bodily fluid. This results in metered diffusion of drug to the local tissue in an amount sufficient to maintain effective anesthesia of the local tissue while avoiding the associated problems of systemic drug delivery. Examples of medical products include anesthetizing cuffs, films or balloons disposed on catheters or tubes; anesthetic (122) coated sutures (120) or the like; adherent anesthetizing bandages, strips or patches, or in the form of an anesthetizing plastisol or foam suitable for topical application. Methods of manufacturing the compound/polymer are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ANESTHETIZING PLASTICS, DRUG DELIVERY PLASTICS, AND RELATED MEDICAL PRODUCTS, SYSTEMS AND METHODS

This application claims convention priority from, and is a continuation-in-part of, U.S. Serial No. 08/622,190, filed March 25, 1996 and Provisional Application, Serial No. not yet received, entitled Anesthetizing Plastics, Drug Delivery Plastics and Related Medical Products, Systems and Methods filed by the inventors on March 7, 1997. Related disclosure will be found in PCT/US94/00492 published as WO95/08305 on March 30, 1995, U.S. Serial No. 126,970 filed September 24, 1993, now U.S. Patent No. 5,417,671, issued May 23, 1995 and U.S. Serial No. 527,593, filed May 23, 1990, now U.S. Patent No. 5,279,594, issued January 18, 1994, each of which is hereby incorporated by reference as if fully set forth, and from each of which the present application, for U.S. purposes, is a continuation-in-part.

According to one aspect of this invention, it has been discovered that anesthetics of amide or ester type, such as lidocaine base, tetracaine base, propafenone or other drugs of similar structure, are highly soluble, or otherwise can be incorporated in large, effective concentrations, in conventional polymers. Under suitable conditions, the drug is found to migrate gradually and steadily to the surface of the plastic. Because of the large concentration found possible, in many cases the percentage reduction of drug present relative to the initial amount of drug, decreases only gradually with time, and provides zero order time dependence in rate over prolonged periods of use. Unique ways have been realized for employing this phenomenon. The plastic is employed as a long-term protective reservoir for the drug. In many advantageous cases, the plastic forms the exterior portion of a functional wall or component of a device as well as serving as a drug reservoir. In other cases fine

particles of the plastic are employed as the reservoir. In important cases the drug is of base form and/or is more soluble in the plastic than in water. In important cases, the plastic is a hydrophobic film-forming or structural resin.

In certain instances, the plastic reservoir material itself is directly exposed to body tissue as in the case of contact with the mucosal tissue or the skin. In certain instances, one or more intervening layers are included to determine release rate to the body or to facilitate transfer of the drug to the body or to isolate the reservoir plastic from contact with body tissue. In certain cases, as in certain dermal applications, the main limit on the dosage rate is the transmissivity of the corneal layer of the skin itself and the reservoir serves to maintain a high or selected concentration of the drug in contact with the skin surface. In other instances, the migration rate of the drug in the resin controls the release of the drug into the patient.

The phenomenon that large concentrations of the drug can be incorporated in conventional plastic resin is found to be especially applicable to FDA-approved structural and film-forming thermoplastics such as fully polymerized polyvinyl chloride (PVC). By the techniques disclosed here and in the preceding patents and patent applications referenced above, PVC in which the drug is incorporated is employed as drug-carrying granules or to coat, print or to form the structure of tubes, films, sheets, bandages, coverings, rods, foams, molded devices, sutures, other medical devices, ingestible formulations, etc.

In a wide variety of important cases the drugs in base form, when used in significant quantities, are found to demonstrate a surprising plasticizing action upon compatible plastic polymers. This facilitates the making of safe, stable and convenient products. The polymer and the drug, alone, without additional plasticizers, forms useful articles in many instances. By selection of the relative proportions of the plasticizing drug and an added therapeutically and biologically inert second plasticizer, the concentration of the drug can be selected, e.g.,

for selection of dosage rate, while maintaining the desired physical properties of the plastic article, such as flexibility and conformability, as in a skin patch or covering.

An anesthetizing or drug delivering effect lasting days, weeks, perhaps even months and years can be achieved by controlling the thickness of the reservoir layer, the concentration of drug present in the layer, and other parameters that govern the particular application.

The products can increase the comfort and ease of drug administration with both prescription and over-the-counter products, and in the case of anesthetic drugs, can reduce the pain of adults and children in many circumstances, reduce hospital stay, increase the use of doctor's office and out-patient care, and increase the efficiency with which medical procedures may be accomplished.

According to one aspect of the invention, it has been discovered that effective concentrations of topical anesthetic compound at contacted tissue, suitable for maintaining topical anesthesia (concentrations that are, generally, extremely large compared to other classes of drugs) can be self-administered by a wall of a medical device by selection of particular materials and particular topical anesthetics that cooperatively meet certain selection criteria. The wall material and the topical anesthetic are selected such that (1) the necessary amount of topical anesthetic "dissolves", i.e. forms a true solution in the wall material, while (2) the topical anesthetic is more soluble in the polymer than in water and (3) the concentration of the topical anesthetic compound in the wall material is such that when the wall is in contact with a body passage, the compound diffuses to a surface of the body at a rate effective in maintaining anesthesia.

The first and third criteria assure that the needed large amount of topical anesthetic can be incorporated and uniformly administered wherever tissue contacts occurs, while the first and

second criteria help to enable criteria 3 to be met by assuring that the topical anesthetic, while effective, neither causes adverse systemic reaction of the patient by too rapid release, nor is waster too soon from the surface of the device if in contact with aqueous body fluid. These three cooperating criteria enable a sufficient concentration of the topical anesthetic to be maintained at the tissue to maintain topical anesthesia for an extended time. Thus, the patient's long term discomfort is successfully eased.

The presently most preferred wall polymer for this aspect of the invention is polyvinyl chloride, while another preferred wall material is vinyl urethane copolymer. The presently preferred topical anesthetic for this aspect of the invention is lidocaine base while dibucaine base also meets the criteria.

Applicant's Example 1 in U.S. Patent No. 5,279,594 dramatically demonstrates the principle. In this case polyvinyl chloride wall-forming polymer and lidocaine base anesthetic are employed. True solution of an effective quantity is achieved by exposing the wall polymer to an atmosphere containing the topical anesthetic sublimed in a vacuum chamber at elevated temperature. Note that lidocaine base is insoluble in water and thus is more soluble in the polymer than in water. This is to be distinguished from the commonly used hydrochloride or salt of this compound which is highly water soluble. The dissolved amount of 550 mg of Example 1 represents a concentration in the polymer wall of 6% (based on the weight, 8 gm, of a #16 urethral catheter); the wall was shown to maintain the anesthesia effect on the tissue. The specification expressly discloses concentrations in the polymer wall that work out to 5% (Example 3) and 10% (Example 4) that are successful in achieving the prolonged level at tissue within the body needed to maintain anesthesia on.

Unlike prior attempts, applicant's solution to the serious discomfort problem is highly practical. The preferred combinations of topical anesthetic and wall polymer that meet the

criteria are all medically acceptable materials. Further, it is found that the common sterilization technique of ethylene oxide can be used with these combinations (claims 2, 6 and 9-11).

In short, the tubes of the invention have a predictable capability to deliver prolonged, effective concentrations of topical anesthetic to the tissue wherever required along the tube length to maintain anesthesia.

Among the aspects shown in the related U.S. Patent No. 5,279,594 are the following.

Tubes have topical anesthetic incorporated in the material of which the wall of the tube is composed, the anesthetic being more soluble in the wall material than in water.

Among the preferred features shown are the following. The base form of the anesthetic is employed. The entire wall thickness of a tube is formed of the anesthetic-polymer material. Materials are employed that enable ethylene oxide sterilizability. PVC and vinyl-urethane copolymer wall materials are employed.

In this first patent disclosure, the placement of an anesthetizing urethral catheter in a patient for eight hours of pain relief is also described. Also, surgery performed with topically anesthetizing endotracheal tubes in dogs is described in which it is shown to be possible to use lower concentrations of general anesthetic because of the local anesthetizing effect of the endotracheal tube.

Use of lidocaine, an acetamide, and dibucaine, an amide are shown. Specific topically anesthetizing products described are a urethral tube, an endotracheal tube, a naso-gastric tube and elastic film of anesthetizing plastic.

A number of methods for making these products are shown in this first patent, including employing a process solution to apply the anesthetic as a film to a preformed structure, from which the process solvent is subsequently evaporated; heating and pressing to cause the anesthetic to enter into solution in the

plastic while forming a sheet or film; and employing gas diffusion transfer of the drug into the plastic resin.

The disclosure of the related second U.S. Patent, No. 5,417,571, discloses further features including the following.

Flexible devices are described in which high concentrations of the anesthetic in base form in the plastic substances perform the function of a plasticizer for the plastic objects.

Further topically anesthetizing medical devices are shown, including nasal tubes, Foley (balloon) catheters, feeding tubes, tubes that pass through the abdominal wall and the peritoneal cavity, and drainage tubes.

Anesthetizing films, cuffs, and balloons are shown as well as loose fitting sleeves that surround medical devices inserted in the body.

The use of a barrier layer that confines the direction of diffusion of the drug from the plastic reservoir is illustrated.

Conversion of a surface layer of the anesthetic in the resin to water-soluble salt form is also described.

Products produced by extrusion and coextrusion techniques are described, as are concentrations of the anesthetic that vary across the thickness of a layer or wall, metering layers lying over the anesthetizing plastic, and use of porsigens in the plastic. Also, incorporation of the plastic in implants and use of the drug such as lidocaine for antiarrythmia medication are described.

The disclosure of the related World Patent application, published as WO95/08305, discloses further use of lidocaine and the like for antiarrythmia and antiseizure treatment. For these uses an orally ingestible form of solid particles of the drug-polymer combination is disclosed with the intention that the particles pass through the gastro-intestinal tract where they release the drug and are eventually excreted.

As now explained herein, propafenone is found to enter solution or otherwise be incorporated in plastic in form enabling it to be orally administrable, or administrable by skin patch, for controlled release for antiarrythmia medication.

Principles of the invention have general applicability to drugs having at least one aromatic ring (substituted or unsubstituted benzene ring) that includes at least one free amide or amine hydrogen in its structure. In particular, drugs having at least one aromatic ring (e.g., at least one substituted or unsubstituted benzene ring), and melting point in the range of the processing temperature of thermoplastic or other heat processable resins, with the drug in base form (e.g., includes at least one free amide or amine hydrogen in its structure), can be dissolved or otherwise incorporated in effective concentrations in heat processable resin, typically at elevated temperature. In many instances, the concentrations of the drug can be very high, e.g. in excess of 10% by weight, in many case preferably in excess of 20% by weight, and most preferably in excess of 30% or 40% by weight. For many conventional low or medium molecular weight resins having processing temperatures between about 250°F and 350°F, numerous of the drugs have been found to be soluble or otherwise capable of incorporation at useful levels. For high molecular weight resins, with processing temperatures up to about 450°F, additional drugs may be dissolved or incorporated at useful levels.

In the cooled form, the solution of resin and drug may behave as they do in conventional plastized PVC, forming, in essence, a solid gel, which, in many useful cases, has a desirable rubbery consistency. In other cases, a network of the drug is distributed through the cooled reservoir resin, in molecular, crystalline or amorphous form, that can be utilized via migration through the resin or by access pathways provided in the reservoir.

In other cases, rather than employ heat processing other techniques, including use of solvents and vapor transfer, are used to incorporate the drug in compatible resins.

In a preferred form, drugs employed according to the invention have the form:

$$Bz - Z - (CH_2)_n - NR^1 R^2$$

where:

Bz is a substituted or unsubstituted benzene ring;

Z is an ester or amide linkage;

and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and N is an integer.

For a desired drug, the resin system is selected to be compatible with the drug such that, at processing conditions and conditions of use, no adverse effects or reactions occur that deprive the drug of its efficacy, or the degree of mobility of the drug desired. For instance, when using thermal processing techniques, the ingredients are selected to withstand the temperatures of processing and the shear forces that are involved in the mixing, milling, or extruding that is involved and to be biocompatible when exposed to the patient.

It has been observed, specifically, according to the invention, that numerous drugs are highly soluble in polyvinyl chloride, chlorinated polyethylene and ethylene propylene, as well as in methyl methacrylate. It has been observed that these drugs have at least one benzene ring, are of base (e.g., free amine or amide) form. They have a lower melting point than the hydrochloric salt form of the drug, that makes them practically processable with thermoplastic resins, e.g. at temperatures in the range of about 250°F to 350°F, and up to 450°F for high molecular weight resins.

As has been previously indicated above, it has been observed that the drugs can have a plasticizing effect on resin.

Broadly speaking, the invention is indicated to be applicable to resins or polymers in which plasticizers can be incorporated or in which phthalates, glycolates or citrate esters are soluble, or in which plasticizers or other additives with at least one aromatic ring can be incorporated.

More specifically, it has been realized that the solubility or ability to be incorporated in resins of such drugs of such molecular structure as described, in a general way, is predictable from the behavior in resins of comparable plasticizers such as phthalate, glycolate, and citrate esters which are also characterized by an aromatic ring. For the class of drugs having an aromatic ring, and especially a single aromatic ring, it can be reasonably stated that such drugs will have solubilities or the ability to be incorporated in the range of plastics in which plasticizers of similar molecular structure are soluble or can be incorporated. Phthalate esters are soluble, or can be incorporated e.g. in polymers and copolymers of polyvinylchloride, chlorinated polyethylene, cellulose nitrate, ethyl cellulose, cellulose acetate, polystyrene, polyvinyl butyryl, acrylic resins, alkyl alkylacrylates, acrylonitrile rubbers, and chlorinated rubbers such as neoprene. Drugs having a single benzene ring and structure similar to the plasticizers are likewise soluble or incorporatable in the range of resins, as a step in the preparation of a drug delivery composition.

Accordingly, further aspects of the invention include the following features. The drug has a single benzene ring; the drug of base form is soluble in resins or polymers in which phthalate, glycolate, or citrate esters are soluble; the drug has local anesthetic properties (whether or not it is generally used as a local anesthetic); the drug is an antiarrhythmic or antiseizure drug having local anesthetic properties; the antiarrhythmic drug is propafenone or lidocaine; the drug is a local or topical anesthetic medication; the drug is an adrenergic

blocking drug such as atenol; the drug is a sympathomimetic drug such as pseudoephedrine, terbutaline or phenylpropanolamine; the drug is an analgesic or antipyretic such as acetaminophen, phenacetin or ibuprofen; the drug is a stimulant of the nervous system, e.g. a psychostimulant such as methylphenidate.

Structurally related drugs may be incorporated in a number of biocompatible polymers or copolymers without preventing the drug from having efficacy. Examples include resins selected from polyvinyl chloride, other polymerized vinyl halides, chlorinated polyethylene, other halogenated polyolefins, cellulosic resins such as cellulose nitrate, ethyl cellulose, cellulose acetate, polystyrene, polyvinyl butyral, alkyl alkylacrylate resins (e.g., methyl methacrylate, ethyl methacrylate), or alkyl acrylates, acrylonitrile rubbers, and halogenated rubbers (e.g., chlorinated neoprene), polyesters such as polyethylene terepthalate, polyamides such as nylon and polyformaldehyde.

Also of consequence is the realization that drugs which have an observable anesthetic characteristic (even if the main use of the drug is not for anesthesia, but for other purposes such as antiarrhythmia or other treatment of the neurophysiological system of the body) can be administered in prolonged manner by resin systems including thermoplastic resin, in which the base form of the drug has been dissolved or is otherwise incorporated.

In certain resins, certain drugs are found to be so highly soluble that the use of relatively low molecular weight resins is possible. For instance polyvinyl chloride with specific viscosity of about 225 (intrinsic viscosity of between about 96 and 99) has been demonstrated to receive in solution as much as 50% of the drugs lidocaine and propafenone. Such resins are preferred when forming tube, sheet-like or fiber material in which considerable flexibility of the tube, sheet or fiber is desired.

For other applications, such as orally administratable granules of fine or coarse powders, it is desired to form an extrusion of the resin with dissolved drug, and then to grind it to form the granules. For this purpose a relatively high molecular weight, rigid resin may be preferred, for ease of grinding. The high molecular weight, long molecules of such resins permit the attainment of higher processing temperatures and longer residence times in the mill or other processing equipment that is employed to dissolve or distribute the drug into the resin. This leads to increase in the amount of the drug that can be incorporated. In turn, this leads to a wider practical range of choice of the resin, permitting use of resins which have other desirable properties, such as meeting requirements of regulatory agencies and the like for prolonged use within the body, as well as to attain desirable process, storage, performance, and economic characteristics.

For those therapies in which more than one drug that is soluble in resin can be selected, another criteria for choice of the system to be employed is the fugitive or diffusive character of the drug within the particular resin. This may be estimated based upon the molecular structure of the drug, the shorter and less complicated the molecule, the more fugitive. For any particular desired therapy, demonstrations with selected drugs and resins are readily conducted to enable empirical observation. Final choice of the constituents and relationships based upon observed, reproducible results is a matter for those of ordinary skill in formulating drug and resin compositions.

As has been indicated, the discoveries described above, which arose in respect of topical anesthetics, have led to the realization that systems of the invention have generality beyond drugs that are known to have anesthetic characteristics. Thus, from the similarity of chemical structure and known characteristics of drugs, plasticizers and resins, it is realized that a wide range of drugs having sufficient unsaturated

moieties, aromatic or heteroaromatic moieties, or similar structure can be delivered employing the present invention. Among these drugs are atenol, pseudoephedrine, terbutaline, phenylpropanolamine, acetaminophen, ibuprofen, phenacetin and methylphenidate.

Thus the present invention teaches and achieves new modes of drug delivery. It enables administration of drugs thought previously to have insufficient half life when administered systemically for particular therapies, and enables delivery, in prolonged fashion, of drugs that heretofore have been required to be administered at disadvantageous frequency or by disadvantageous modes.

In another aspect, the present invention teaches the applicability, in a new way, of general knowledge of the plastics industry as to compatibility of particular plasticizers, solvents, and other additives with known structural and film forming plastic systems. The molecular structure of the base form of a drug having a benzene ring, that is desired to be delivered, is compared with the molecular structure and concentrations used of proven plasticizers, solvents or additives for plastics systems. On the criteria of the similarities, a small group of candidate resins is identified. Simple mixing and heating of a substantial concentration of the drug with the resin, as between two plates under pressure, identification of the better combinations for compatibility of the introduced materials and enables observation of the efficacy of the system. In the case of topical anesthetic products, efficacy is readily observed based on the onset time for numbness, and the degree of numbness achieved. In other cases, migration of the drug from the novel reservoir through cadaver tissue can be observed.

To further expand upon the applicability of prior knowledge, in respect for instance of polyvinyl halide products, one should consult the literature beginning with U.S. Patent Nos. 2,188,396

and _____ to Waldo Semon, the discoverer of soluble plasticizers for polyvinyl halide products. The disclosure of those patents is hereby incorporated by reference. Such references further indicate the plasticizer or solvent compositions with which drugs for a vinyl system can be compared. Consulting the literature readily provides similar references for other candidate resin systems in light of the present teachings.

The drug compositions according to the inventions are formulated to advantage in various ways. Resin granules are prepared such as fine or coarse powder in tablet or capsule form suitable for oral administration. The resin in orally administratable form has characteristics whereby the drug is released in the stomach and/or in the lower portion of the gastrointestinal system after which the resin is eliminated through the bowel. A protective coating on the particles may be employed to protect the composition from the acidic portions of the gastric tract.

The resin may be selected out of safety and regulatory considerations to reside as an implant or covering for prolonged periods in contact with tissue or body fluid; thus the resin may be formed as a thin, flexible wall or fiber strip or rod exposed to contact tissue; the resin is configured to perform an added function, e.g. to perform the added function of a fluid-contacting tube, feeding tube, drainage tube, or an irrigation or fluid drug administration tube or the covering of an endoscope or other examination device

In some cases, the resin is loaded with (has dissolved or otherwise incorporated in it) a plurality of drugs, wherein the plurality includes drugs that have the same or different properties.

The resin also is advantageously configured to deliver local or topical anesthetic in the exterior region of an incision or wound, e.g. the resin is configured to form a functional bandage or compress.

Another aspect of the invention is a wound or incision-contacting device formed to reside beneath the closure of a surgical point, and formed at least in part of thermoplastic resin in which a topical anesthetic or other drug is dissolved or otherwise incorporated according to the invention. Such a device can reduce local pain and discomfort and promote healing.

Certain preferred embodiments of the wound or incision-contacting devices have one or more of the following features.

The device includes a drug in base form dissolved in resin and in water soluble salt form associated with the resin. The salt form is a hydrochloride salt. The device includes hydrophobic resin in which the base form is dissolved and in which the salt form is imbibed in aqueous solution in porsigens or other receptive portions or is in the form of crystal deposits that result from imbibing and subsequent drying. The device is a tube having a surface that contacts tissue to be treated. The device is a film having a surface that contacts tissue to be treated. The device is present in a compress or bandage. The device is formed at least in part of thermoplastic fibers in which the drug is present. The device is a suture formed at least in part of thermoplastic resin in which the drug is dissolved or otherwise incorporated. The fibers are at least part of a textile material. The material is a non-woven. The fibers are hydrophobic. The hydrophobic fibers are combined with hydrophilic fibers that contain an aqueous substance that promotes release and transport of the drug from the hydrophobic resin. The device comprises a cotton or other absorbent material upon which is applied, e.g. by printing or coating, in a pattern a polymer in which the drug is incorporated. The device is combined with a fluid, ointment or adhesive that promotes transport of the drug. The fluid, ointment or adhesive contains a drug, and the drug from the resin is effective to replenish the drug in the fluid, ointment or adhesive. The drug in the fluid, ointment or adhesive and the drug dissolved or incorporated in the resin include topical anesthetics. The fluid, ointment or

adhesive includes surfactant or other permeation enhancers that promote diffusion of the drug through tissue, such as the skin. The fluid, ointment or adhesive includes a thickener. The fluid, ointment or adhesive includes carboxypoly methylene (Carbopol™). The fluid, ointment or adhesive that cooperates with the drug dissolved or otherwise incorporated in the resin includes a combination of topical anesthetics and an emulsifier such as Tween™ (a polyoxyethylene fatty acid ester). The combined anesthetics in the fluid, ointment or adhesive are prilocaine and lidocaine.

Another aspect of the invention is a wound or incision treating device comprising fibers or constituents of hydrophobic resin in which a drug, and especially an anesthetic base, is dissolved.

Another aspect of the invention is a wound or incision treating device comprising fibers or constituents of hydrophilic resin in which a salt form of anesthetic is imbibed or deposited as crystals.

Certain preferred embodiments of these aspects have one or more of the following features. The device comprises a combination of fibers or constituents of hydrophobic and hydrophilic resin. The fibers or constituents of both types of resin carry a drug. An aqueous solution in the hydrophilic fibers is adapted to assist in transport or migration of base-form drug in the hydrophobic resin. The aqueous solution in the hydrophilic fibers is acidic and adapted to convert the base form of the drug to a water soluble salt.

Topically anesthetizing plastic fibers, sutures and textile layers, functional bandages and compresses and methods of manufacture of such devices are also provided.

Additional important features of the invention include transdermal patches employed to apply topical anesthetic or drug to or through the skin, use of high concentrations of lidocaine as a tackifier to form a tackified methyl methacrylate-based

adhesive useful as a transfer layer or as a significant drug releasing reservoir, use of plastisols for fabricating products including sheets, foams, films and coatings, formation of adherent and lubricious anesthetizing coatings and formulation of creams and other liquid suspensions and adhesives that employ solid plastic particles of e.g. PVC, in which a drug such as lidocaine is present. A drug delivery or anesthetic delivery foam ear plug, foam nasal plug, foam drug or anesthetic delivery rectal, vaginal or other suppository, a dental appliance, a sublingual or boccal insert, and anesthetizing hot water bottles, ice packs and cushions are disclosed.

Drawings

Figure 1 illustrates a greatly magnified view of a fiber in which a drug is dissolved;

Figure 2 diagrammatically illustrates a portion of the fiber magnified still more;

while Figure 3 illustrates a spinnerette for forming the fiber.

Figure 4 and 5 illustrates the process of forming a non-woven using fibers according to Figure 1.

Figure 6 illustrates a bandage or compress formed of the non-woven of Figure 3, while Figure 7 shows a treatment of a non-woven.

Figure 7 and 8 show the formation of sutures according to the invention.

Figure 9 diagrammatically shows a compress according to the invention.

The drawings and descriptions of the above-referenced published patents and applications are also incorporated by reference.

Description of Embodiments

In an important embodiment, propafenone base in effective quantities is dissolved or otherwise incorporated in a resin, and

especially a hydrophobic, thermoplastic resin, in a manner adapted for exposure to the body under conditions in which propafenone in the resin is gradually released into the bloodstream. In one case, in the course of manufacture, propafenone is dissolved in orally administratable solid granules such as coarse or fine powder of non-biodegradable thermoplastic resin. The drug passes through the wall of the gastric tract and into the blood stream. The blood flow then transports the released propafenone to the site at which the drug is effective, e.g. to reduce, treat, or block arrhythmia. In another embodiment, the resin is formed on or as an implant to release the drug directly to heart tissue or the blood stream, or as a transdermal patch or as a drug-applying ear or nose plug. (In the foregoing embodiments lidocaine can be substituted for propafenone.) For demonstration of solubility in resin, propafenone base has been dissolved in a concentration of 50% by weight in intermediate molecular weight polyvinyl chloride, and in concentration of 10% in chlorinated polyethylene. In this and other systems described, when resins are employed in which the solubility of the selected drug is relatively low for the particular therapy desired, a high molecular weight polymer can be selected to provide a higher processing temperature and longer period for the manipulation of the resin and drug in a mill or other processing machine, without degradation or volatilization. These conditions increase the amount of drug that can be incorporated in the resin without degrading the resin, and the relative rigidity of the resin can assist in its grinding to form granular particles or powders.

In one approach the carrier is adapted to provide sustained release in portions of the body where propafenone base or lidocaine base is exposed to alkaline conditions, for instance in the lower intestine. The carrier may reach the lower intestine by oral administration and passage through the stomach. It may be coated with a time-dissolvable or acid-dissolvable protective layer that protects the base form of the drug as the material

passes through acidic regions of the gastric system. For this purpose the PVC or other thermoplastic material in which the drug is dissolved may be in the form of orally administered granules in which the propafenone or lidocaine is dissolved, the granules being covered with the protective coating.

An outer layer or protective coating may contain propafenone or lidocaine base which is converted into effective quantities of propafenone or lidocaine chloride during passage through acidic regions of the stomach.

In another case, the concentration of the propafenone or lidocaine dissolved in the PVC itself may be greater near the surface of the granules, or otherwise disposed so that some of the propafenone or lidocaine is removed while exposed to acidic conditions, but an effective concentration remains in the granules as the granules reach the lower intestine.

The particular concentrations of propafenone or lidocaine to employ in the resin can be determined once the parameters of the mode of administration have been selected, e.g., selection of the physical form of the delivery carrier and the point and nature of the absorption to be employed. The effective levels of propafenone or lidocaine in the bloodstream for the antiahrrythmia and antiseizure treatments is already known to the medical field.

Turning now to the figures, in Fig. 1 a fiber 100 of thermoplastic resin is represented on a much enlarged scale. A small section of the fiber is shown in a still more enlarged scale in Fig. 1A in which stippling denotes anesthetic base or other drugs in solution or incorporated in the resin. Certain fibers of this construction are characterized as having been formed by extrusion and drawing of thermoplastic synthetic resin in which was dissolved a drug having an aromatic ring and which is soluble or capable of otherwise being incorporated in the resin. Other fibers of this construction are characterized as having been formed in similar manner, but of thermoplastic resin

not containing the drug. Following forming the fiber, either the fiber per se or when formed with other fibers into a fabric, suture, or the like, the formed device is exposed to the drug under conditions promoting the drug entering into solution in the body of the fiber. For instance, the drug may be provided in a suitable process solution that promotes entry into solution of the drug into the resin, e.g. in the case of fibers of polyvinyl chloride resin, a 50% lidocaine base in solution with 50% ethyl acetate may be employed.

In Fig. 2 a tiny spinnerette nozzle 101 is diagrammatically illustrated from which a fiber 100 is extruded from feed stock comprising a drug having an aromatic ring dissolved in a thermoplastic resin in which it is soluble. Alternatively the fiber may be formed without the drug being in the extruded resin.

In Fig. 3 a non-woven fabric 102 is formed by the well known spun bonded process employing spinnerettes according to Fig. 2.

In Fig. 4 a non-woven fabric is formed by the spun bonded process employing spinnerettes 101 according to Fig. 2 and additional spinnerettes 103 from which hydrophilic fibers are extruded, to form a composite non-woven fabric.

In Fig. 5 is shown a bandage or compress comprised of layers of non-wovens according to Figs. 1-4.

In Fig. 6 is shown the post-forming treatment of the non-woven 102 of Fig. 3 in which drug at the surface of the fibers is converted to water soluble salt form by immersion in a slightly acid bath followed by drying 120.

Fibers, threads, yarns, continuous films or perforated films or strips of plastic resin in which the drug is dissolved or otherwise incorporated may likewise be treated.

In Fig. 7 a suture 130 is shown on greatly enlarged scale formed of filaments according to Fig. 1 that have been subjected to a crimping process to impart knottability to the filaments 100' that comprise the suture.

In Fig. 8 a suture is shown formed of crimped filaments 100' according to Fig. 7 and crimped hydrophilic filaments 107.

The sutures of Figs. 7 and 8 can be formed by coating tensile members, such as silk or glass, with the resin containing the drug.

In Fig. 9 is illustrated a compress 120 containing topical anesthetic associated with an ointment 122 that serves as a transfer layer for the anesthetic from the compress to a healing surgical site 24.

Preferred embodiments of the compress are an assemblage comprised, at least in part, of thermoplastic resin components in which an anesthetic base is dissolved or otherwise incorporated or in which a drug of similar structure in base form, having healing properties, is dissolved.

The thermoplastic resin containing the drug serves as a long term reservoir to dispense the drug to an ointment, from which the drug is transferred to the body. Preferably the ointment contains a surfactant or other agent that promotes penetration of the skin, to aid in passage of the drug. The ointment itself can contain anesthetic in base form, and may advantageously contain an emulsifier where both oily and watery constituents are present. The ointment may contain a mixture of lidocaine hydrochloride and prilocaine base.

Certain embodiments of this aspect of the invention have one or more of the following additional features.

The compress is formed of a bat of fibers at least some of which are thermoplastic fibers in which the drug is incorporated or applied. The bat of fibers includes hydrophilic fibers. Alternatively, a bat of hydrophilic fibers carries a deposit of resin containing the drug, as by printing an array of dots or a reticulated pattern of lines, between which areas of hydrophilic fibers are exposed. Alternatively the compress is formed of a non-woven fabric of fibers at least some of which are thermoplastic fibers in which the drug is incorporated. The non-woven fabric includes hydrophilic fibers. And in still another alternative, the compress includes a gel or gel-like

substance that includes a constituent comprised of hydrophobic thermoplastic in which the drug is incorporated. The constituent may be a film, shredded film, fiber or granules of the thermoplastic in which the drug is incorporated.

In still another embodiment, the compress comprises collagen alginate dressing containing powder granules of hydrophobic thermoplastic in which the anesthetic is dissolved.

Benefits of Pain Relief System of the Invention and Further Examples

The invention has very important advantages for dermatology and dermatological surgery, and for taking skin for graft purposes, and has very wide applicability in general surgery, and surgery of other specialties.

One important aspect of the invention concerns preemptive anesthesia. Medical research has indicated there are benefits in employing presurgical local anesthesia even in cases where general anesthetic is to be administered for blocking the central nervous system. It has been shown that concurrent local anesthesia avoids shock to the peripheral nervous system, promotes healing, and helps avoid persistent sensitivity of the surgical area after healing has occurred. The products described can have a desirable pre-emptive anesthesia effect. Local anesthesia during the painful recovery period achieved with the same products can likewise reduce sensitivity of the eventually healed area.

The pre-emptive effects and many other benefits of prolonged local pain relief using the novel topically anesthetizing plastic are illustrated by the following idealized scenario.

Scenario

The patient is examined using an endoscope that has an anesthetizing covering formed following the teachings of the invention.

A patient is scheduled for surgery. Under physician's instruction, the patient, at home, applies an anesthetizing plastic preoperative covering to the face, chest, abdomen, back or other area where the surgery is to occur.

This is done simply by pressing a self-adherent or otherwise secured film, sheet or foam of anesthetizing plastic upon the skin, or by applying a fluid composition that forms a long-acting anesthetizing film, or by applying a cream or coating containing fine anesthetizing plastic particles, such as solid PVC particles, in which the drug is present in solid solution or is otherwise incorporated.

The patient arrives at the hospital with the surgical site numb.

Prior to surgery, without pain, blood samples are taken or injections are made with needles in the anesthetized area of the patient.

Also, prior to surgery, the patient is prepared for general anesthesia by having an endotracheal tube placed in the trachea. Both the tube and the film-formed cuff of the endotracheal tube have anesthetizing plastic surfaces exposed to the tracheal tissue which numbs very rapidly.

General anesthesia is then administered to the patient, but a relatively light level can be used, and dosage of muscle relaxants can be limited, because of the topically anesthetizing endotracheal tube. Anesthesia of the tracheal tissue assures the anesthesiologist that the patient will tolerate the tube throughout the surgical operation and during recovery. Following the surgery, the light level of general anesthesia and limited use of muscle relaxants, made possible by the anesthetizing tube and cuff, results in faster awakening of the patient and fewer side effects.

During surgery, one or more flexible anesthetizing drain tubes, strips, threads, rods or devices appropriate to the surgical site are temporarily implanted in proximity to nerves that have been disturbed. This may be done e.g. in the posterior

gutter of the chest or next to nerves in the peritoneal space or the peridural space, etc.

Under the closed incision the surgeon leaves an anesthetizing drain tube or an anesthetizing strip, rod or fiber. The surgeon employs sutures that have an anesthetizing exterior, and applies an anesthetizing absorptive compress upon the closed surgical site.

During recovery the patient can tolerate the deep pain produced by the surgery and the presence of foreign devices without heavy doses of morphine or similar sedations, because of the action of these devices.

As a result during recovery, the patient remains alert, rapidly re-establishes normal bodily functions, and requires less attention by hospital staff than has often been the case.

In many cases the patient can be sent home early, as the incision is relatively pain-free. Implanted anesthetizing devices are left in the patient's body when the patient goes home, to be removed later when the anesthetizing sutures are removed. During convalescence anesthetizing plastic hot compresses or hot water bottles, ice packs and foam cushions are employed.

The sutures and the drains, strips and other devices that were left in the body are removed by tension applied to the devices. Fiber reinforcement in the devices assures that the devices do not break. Because of their continued anesthetizing effects, little pain is experienced as the devices are withdrawn, even if adhesions have begun to form.

In some cases, for instance in the case of pancreatic cancer, permanent or semi-permanent anesthetizing implants of selected shape are left in the body long-term to ease the pain of the patient.

The skin over the healed incision is not sensitive due to the strategy of employing pre-emptive local anesthesia combined with general anesthesia.

Prolonged local pain relief products realized according to the invention thus have many roles to play in surgery.

Other uses in the fields of allergy, anesthesiology, burn treatment, cardiology, dentistry, dermatology, gastroenterology, neurology, oncology, orthopedics, pediatrics, podiatry, urology, veterinary medicine and numerous other branches of medicine and personal care are illustrated further below and in the referenced patents and applications, or will be apparent to those of ordinary skill.

HOME AND PERSONAL USE

The cook with the burned finger applies an anesthetizing plastic strip and proceeds to complete dinner preparations, as the pain subsides.

A child cries "Mommy I have an itch". A spot-size, adherent, non toxic anesthetizing plastic bandage, made pursuant to the invention, is applied with a kiss and the child's discomfort is soon relieved.

The child with a bad scrape has an anesthetizing plastic strip applied and returns to play.

The athlete applies an ice pack or a water bottle having an anesthetizing outer covering.

DEMONSTRATIONS

As indicated above, lidocaine base and other anesthetic bases of amide type and ester type have been shown to act as plasticizers of PVC and other plastic resins such as CPE (chlorinated polyethylene) and EP (ethylene propylene). Both EP and CPE have been processed to hold about 25% lidocaine base by milling, while PVC has been processed to hold about 50% of lidocaine base. The polymers release lidocaine to their surface to produce a prolonged anesthetic effect. The rate at which migration occurs varies from plastic to plastic, a phenomenon which can be used to advantage to establish the proper drug delivery rate for the desired application.

Anesthetic bases also demonstrate marked solubility in many methacrylate polymers and serve in high concentrations to make the composition tacky as an adhesive that is employed to place the anesthetizing plastic reservoir material in close conformity to the skin.

Most of the following demonstrations employ PVC (fully polymerized polyvinyl chloride and lidocaine base, both of which are FDA approved products, known for their biocompatibility under many conditions such as medical tubes and skin patches. Likewise, methacrylates are approved for instance as bone cement and for topical adhesives.

Solvent-based articles have been fabricated employing solutions of PVC, as well as other resins, and lidocaine base in process solvents such as THF (tetrahydrofuran), cychlohexanone, and toluene. These solutions, containing the plastic resin and lidocaine, have been printed or painted on cotton gauze, and on the exterior of silk suture, vinyl endotracheal tubes, Foley catheters, naso-gastric tubes and other devices to provide bodily tolerance to these articles. The process solvents are removed by evaporation leaving the anesthetic incorporated in the polymer layer.

A use of such a solvent-based coating system is the coating of large concentrations of local anesthetic base in methacrylate plastic upon a carrier backing to provide anesthetizing patches for the skin. In cases where the carrier backing is PVC, the backing serves as a reservoir and the adhesive coating can be thin as its function is only to serve as an adherent and transfer layer, and not as the principal reservoir or as a metering layer.

As another manufacturing approach, in many cases found to be better than solution coating, useful products have been produced in a milling operation by combining lidocaine base with PVC between two hot rollers, with the addition of heat stabilizers to prevent discoloration at 340° F during milling. Both E.P.O. (soy) and Ca-Zn heat stabilizers, which been employed, are F.D.A. approved for medical devices.

Laboratory demonstrations using these and other methods of application have shown that lidocaine base and other amide and ester type anesthetics, in sufficient concentrations, are potent plasticizing agents for polyvinyl chloride and other plastic resins. For instance, lidocaine added to polyvinyl chloride is all that is needed to create a soft, stretchy, elastic vinyl milled film or sheet. Like the common vinyl plasticizer di-isooctyl phthalate, lidocaine base slowly migrates to the surface of the formed object, to serve as a sustained source of anesthetic to tissue contacted by the device. The rate of drug delivery is governed by the selected concentration of the drug, the selected plastic resin and the acceptance rate of the part of the body with which the anesthetizing plastic is in contact. In the case of lidocaine, upwards of 50% by weight in solution in PVC can be employed. A piece of such milled vinyl anesthetic material has remained taped to skin for 10 days without any diminution of anesthetizing effect or apparent loss of plasticization.

With PVC-lidocaine products, topical anesthesia is provided to any mucous membrane or body cavity lining within five minutes by an article constructed of a 50%-50% by weight PVC-lidocaine base composition. With this system, adult skin requires less than between one and two hours of direct contact for onset of anesthesia, depending upon the type of anesthetizing plastic selected, presence of enhancers, and surface preparation. Numbing of the skin (hypesthesia) is found to be accelerated by the action of penetration promoters. For instance, if the skin is first washed with an enhancing agent such as lauryl alcohol, oleyl alcohol, ethyl oleate, or nonionic surfactants such as dimethyl lauramide, faster onset is achievable.

Process solution techniques of applying the drug in solution to a PVC substrate, or a drug-PVC composition to PVC or other substrates are applicable to pre-formed objects and carrier sheets, by simple coating, painting or spraying techniques.

Milling has the advantage over such process solution techniques in not requiring volatilization of a process solvent. Products similar to milled products can be produced by die extrusion techniques in cases where sales volume warrants the investment or in cases where tube or other profiles are desired. Vinyl and lidocaine withstand the temperatures and shear forces associated with milling and extrusion without breakdown or detrimental reaction. The cooled product is found to be flexible, biocompatible and efficacious.

By mixing solution grade PVC powder and lidocaine as by a Henschell mixer, it is found that a sufficient temperature may be achieved under mixing conditions to enable the lidocaine to enter into solution in the PVC without reaching the melting point of the lidocaine or the PVC. Under such conditions an anesthetic base-PVC combination possesses the advantage of not requiring a heat stabilizer in processing.

It has been further discovered, however, that a plastisol approach in many instances offers important advantages over the other techniques. To achieve a low temperature plastisol a low concentration of a suitable alcohol is included to form a plastisol composition, for example the plastisol is formulated with lidocaine base, polyvinyl chloride and an alcohol such as lauryl or oleyl alcohol.

Also for a low temperature plastisol, a composition can include prilocaine in combination with lidocaine and PVC. Lidocaine base (a crystalline white substance at room temperature) is very soluble in prilocaine base (an oily liquid). A 50%-50% oily liquid eutectic mixture forms a pourable plastisol when mixed in equal amounts with solution grade PVC, with no other ingredients. Prilocaine has the potential disadvantage of producing methemoglobinemia in large systemic dosage. In many circumstances it is not expected that blood levels would prove to

be dangerously high with topical anesthetic devices fabricated by this technique.

A plastisol formed with the combination of lidocaine and one of the alcohols just mentioned, and PVC of solution grade, or with prilocaine as mentioned, is screen printed on cotton surgical gauze and then heated to about 275°-300° F briefly to form a spot form or other pattern of anesthetic coating. The gauze portions not coated provide for absorption of blood and exudates; the printed pattern of congealed anesthetic plastisol alleviates pain from a surgical incision, laceration, or burn.

Lidocaine-PVC plastisols also are utilized to create pain relieving devices as when the plastisol is molded to form the device or is coated on a preformed device. A vinyl penrose surgical drain coated with the plastisol, and suitably heated to congeal the plastisol, can be positioned in an abdominal incision to relieve pain mediated from sympathetic pain endings in the peritoneum. A chest tube coated on its distal 4 inches can be positioned to keep intercostal nerves anesthetized post thoracotomy. A Foley catheter coated with an anesthetic plastisol can relieve catheter discomfort. A drainage tube formed entirely of the plastisol is formed by coating the plastisol on a tubular mold, heating the plastisol to congeal it, and stripping the tube from the mold by a rolling action.

A plastisol pain control device is extruded as a layer around a polyester, silk, or glass thread and heated to form a strong composite fiber for placement in the peridural space. The internal fiber provides tensile strength for enabling removal by application of tension to the portion of the device remaining out of the body. Sutures (such as silk) coated with a PVC-anesthetic plastisol reduce pain while in place and during removal. Early discharge of the patient can be made easier to accomplish if skin and sympathetically mediated pain is relieved or eliminated for several days subsequent to major surgery by such devices.

Plastisol Example I

An anesthetic-plastic plastisol is created using oleyl alcohol as a dispersant as well as plasticizer. The alcohol disperses the aggregated PVC particles and the lidocaine particles and brings them into intimate contact with each other.

A mixture of 15% by weight oleyl alcohol with 42.5% by weight lidocaine base and 42.5% by weight emulsion grade polyvinyl chloride, is formed by adding the alcohol after a mixture of the latter two ingredients is heated to about 340° - 350°F. With grinding, stirring and persistent agitation a fluid is formed that is painted on an aluminum foil and placed in oven. A film is created at 300°F in about 2 or 3 minutes. The film is tough, elastic and stretchy and has marked topical anesthetic properties over a period of time when applied to the skin. In similar fashion the plastisol is knife coated to a uniform thickness upon a substrate, followed by heating to congeal the resin. In another case, the plastisol is poured into a mold to provide a product of a desired functional shape.

Plastisol Example II

The plastisol of Example I is formed into a cord, a tube and a penrose drain by forming a sheet and heat sealing it to form a tube or solid cylinder.

A tube is formed by painting the plastisol over a piece of glass tubing that serves as a mold. The painted mold is heated by heatgun or oven to congeal the plastisol and the resultant tubular layer is then stripped by rolling from the mold to provide a thin-walled tubing for use as a drain. The tube is useful for instance to drain the peritoneum and provide anesthesia at the sympathetic nerves related to the peritoneal cavity.

The plastisol is also injected with a syringe into a section of silicone tubing. The silicone tubing is placed in the oven at 300°F to cure the plastisol. The tube is removed by cutting with

a sharp instrument, and the remaining central core of cured anesthetic plastic plastisol comprises a flexible anesthetic rod or cord depending upon the size of the mold tube.

Plastisol Example III

A Foley catheter of vinyl is painted with the plastisol of Example I and cured by application of heat with a heat gun that heats the superficial areas of the device without damaging the structure of the catheter.

Application of the plastisol to a preformed object made of vinyl provides compatibility of materials that ensures a good bond.

For applying the plastisol to preformed objects of other materials, an intermediate layer, e.g. a thin layer of methacrylate adhesive, is applied to achieve better bonding of the anesthetizing plastic.

Reinforced rods or fiber are created by first pulling glass fibers through a section of silicone tubing, subsequently pumping the plastisol of Example I into the tubing and curing the assembly with heat. The curing PVC-lidocaine plastisol binds to the glass as the result of applying a roller to the exterior of the silicone tubing to assure that the plastisol is thoroughly integrated into the pores of the glass fiber. The resultant rod or fiber has tensile strength that enables it to be removed from the body by application of tension.

Plastisol Example V

The plastisol of Example I is screen-printed as an array of spaced spots on a cotton gauze square and cured with heat. The gauze square has anesthetizing properties. Placed over a wound it numbs tissue while absorbing fluids from the wound.

Plastisol Example VI

A plastisol is made of a mixture of 25% prilocaine, 25% lidocaine and 50% polyvinyl chloride, by weight. The combination

is a thick liquid that is readily paintable or applied as coating or used as a silk screen printing fluid. In the example it is painted on selected objects and heat cured to form a very tough tenacious coating that is very easily handled. The resultant product has excellent topical anesthetizing properties.

Plastisol Foam Example VII

Foam is formed from the plastisol of Example I by adding between about 2 1/2 to 5% foaming agent, such as sodium bicarbonate, to the plastisol. The concentration of foaming agent is selected in accordance with the desired foam density. The plastisol is cured by heating to 350°F as before. To prevent discoloration it is advantageous to add 1 or 2% of zinc calcium heat stabilizer or soy stabilizer.

Resultant foams range from very hard to relatively soft. Other blowing agents, such as halogen compounds, are also used to form anesthetizing plastic foams.

As with the preceding example, various forms of anesthetic base-PVC combinations lend themselves to foaming with sodium bicarbonate and other blowing agents. Foams with a well formed outer surface establish skin hypesthesia rapidly and provide a mechanism for providing uniform compliant skin contact. Foams formed at relatively high temperatures typically require heat stabilizers in their composition. They can be formed with lidocaine-alcohol PVC plastisols or lidocaine-prilocaine-PVC plastisols or they can be formed by milling techniques.

Plastisol Molded Foam Example VIII

The plastisol of Example I or the plastisol of Plastisol Example VI is made into a molded foam object by the technique described in Plastisol Foam Example VII. When sodium bicarbonate (or other foaming agent) and heat stabilizer are added to these plastisols, foam is produced at about 350°. A starting layer a

few thousandths of an inch thick expands remarkably to between 5 and 10 times its preheated thickness.

The plastisol or mixture is poured into a mold of selected shape and heated to cause foaming to fill the mold and produce a foam shape of anesthetizing plastic as determined by the mold. This technique is employed with molds suitable to form drug delivery or anesthetizing plastic articles. These include foam ear plugs, foam nose plugs, or foam rectal or vaginal suppositories, sublingual or boccal inserts, cushioned surfaces for prostheses, and other foam objects comprised of anesthetic plastic foam or drug delivery plastic foam.

PVC anesthetic base devices are not intended for total absorption or to be metabolized by the body. However, by introducing a length of a suitably sized tubing, rod, fiber or molded plastisol device next to pain conducting nerves, prolonged blockade of those nerves can be effected for hours, days, or weeks. The emergent end of the device can be secured with adhesive tape and removed painlessly when appropriate. Techniques for introducing a fiber in the body are well established (utilizing endoscopic, large bore needle or open surgical techniques).

Tapes, Coverings and Patches

PVC-anesthetic base tapes are simple to form. Tapes with a vinyl component, or tapes coated with methacrylate adhesive, can be mechanically coated at room temperature with either a solution of solvent (ethyl acetate) - lidocaine base or an alcohol-lidocaine base solution followed by heat curing. The anesthetic agent is absorbed by the skin and makes the tape capable of numbing skin after contact of an hour or two. Tapes treated with dilute concentrations of anesthetic soluble in the tape structure or its adhesive renders such tapes less painful when removed from hairy or sensitive body areas.

Tapes, and film and sheet coverings may be formed by milling or extruding 50-50 lidocaine PVC compositions as previously

described, using plastisols. Such coverings, with or without intervening adhesive or transfer layer, can provide a desired partial numbing effect on burns and areas affected by post herpes neuralgia. Where the coverings are moisture impermeable, retained perspiration on the skin enhances the permeability of the skin to the delivered drug. In such cases, the sheet or tape serves both as the drug reservoir and as the occlusive covering.

A form of methacrylate (available as a spray adhesive from the 3M Corporation) has proven to be useful as a component to demonstrate a device to anesthetize small or large areas of human skin. Lidocaine base has been found to be soluble in high concentrations in the solids component of 3M's #77 spray adhesive, for instance. When the solids component of the adhesive spray (about 30-35% of the spray mixture) is mixed with about 33% lidocaine base, a stable, tacky contact adhesive is formed, due to the effect of the large concentration of lidocaine in the resin. The composition has marked topical anesthetizing properties. The lidocaine acts in a manner similar to its role as a plasticizer to assist in rendering the solids tacky. When the lidocaine concentration in the mixture is increased to 50%, a super-saturated condition prevails, and in a matter of a few hours the excess lidocaine base crystallizes and the adhesive becomes substantially less tacky at room temperature. However, when this adhesive-topical anesthetic mixture is applied to polyethylene film as a carrier and is pressed with a warm hand to human skin, sufficient tackiness is observed that the film clings to the applied areas effectively, but can be readily removed. The tacky product is suitably dispensed with the tacky layer protected by contact with silicone coated release paper.

In another instance a vinyl tape having anesthetic base incorporated serves as a reservoir and a thin layer of methacrylate adhesive applied to the tape serves to adhere the tape to the skin and act as a transfer layer deliver the anesthetic to the skin as it is resupplied by the reservoir.

With such devices, in 1-3 hours topical anesthesia of the skin is established, which will last for 2-3 days if the film patch is left in place. Washing the skin e.g. with lauramide surfactant prior to applying the film decreases the onset time for skin anesthesia. The topical device is easily and painlessly removed with little transfer of adhesive. After removal, anesthesia has been found to be maintained for about 30 minutes. If longer acting anesthetic bases (such as dibucaine) are employed instead of lidocaine, anesthesia is found to last substantially longer following removal. During this interval minor plastic surgery, electrolysis, laser treatment to remove hair, cryosurgery, dermabrasion, or application or removal of tattoos is performed painlessly.

Film patch anesthesia is accomplished with a surprisingly low dose of local anesthetic, about 7 mgs./inch^2. A 2 inch X 4 inch patch contains about 56mgs, of lidocaine base, (one gram of lidocaine distributed over one square foot of film). This amount of local anesthetic is found to anesthetize a skin area for about 1 to 2 days. This contrasts with Astra Emla® cream which utilizes approximately 250mgs. of eutectic prilocaine-lidocaine retained under an inconvenient occlusive dressing.

Skin Patch Example I

A sheet was prepared from a plastisol consisting by weight of 42.5% lidocaine base, 42.5% emulsion grade PVC and 15% oleyl alcohol.

To prepare the plastisol, the three ingredients were stirred with mortar and pestle until homogeneous. The mixture was spread on an aluminum sheet and cured at 300°F in the oven.

This produced a rubbery, stretchy, tough sheet of clear plastic which over many days became opaque on its surface, but remained flexible.

This sheet was employed as a skin patch by placing a 1 inch square patch on the back of a hand held by a piece of adhesive tape lying over the patch. The product, prepared as a finger

bandage, has the center compress layer of a conventional plastic strip bandage replaced by the cured plastisol layer.

When held against the skin for about an hour and a half or two hours, total anesthesia was observed under the contacted area. Onset was accelerated to an hour to an hour and a half by applying Betadine surgical scrub mixture before applying the patch. Betadine is a mixture of povidone iodine complex in water solution with anionic and ionic surfactants (lauramide DEA).

Such an enhancer can be applied either directly to the skin as a prep before applying the anesthetic plastic layer or dried Betadine may be provided on the layer itself, which is moistened before applying the patch.

The effect of the scrub solution is to sterilize the surface and to accelerate the absorption of the local anesthetic and the numbing effect. Lauramide enhancers have a similar effect.

Skin Patch Example II

A film of lidocaine base, PVC and polyethylene oxide (PEO) was prepared. In one case a film of 43% polyethylene oxide, 32% lidocaine base and 32% polyvinyl chloride was prepared by mixing the dry ingredients and placing the mixture in an oven at 300°F to convert the mixture to a film. In another case a film was prepared with process solvent techniques using methylene chloride and tetrahydrofuran as process solvents. Methylene chloride dissolves the PEC, tetrahydrofuran dissolves the polyvinyl chloride. Both solvents dissolve the lidocaine. After coating, the process solvents were removed by volatilization.

Films formed each way are placed under an occlusive dressing or under a piece of tape, attached as the compress of a finger bandage that has pressure-sensitive adhesive holding strips, or held by other means in constant contact with the skin. Anesthesia develops in 1 to 2 hours. If Betadine is placed under the film, the onset of anesthesia is accelerated to about 1 hour.

By holding such a film intimately in physical contact with the skin and keeping it covered to prevent loss of moisture, retained perspiration within the skin provides sufficient concentration of water to maintain the hydration of the PEO, and maintain the intimacy of contact between the skin and the film.

As long as the film is kept in contact with pressure, as by pressure sensitive tape, anesthesia is maintained for 10 days.

In other examples, skin patches can employ other water based adhesive systems to hold the solid vinyl drug containing particles intimately to the skin. Such adhesive systems are described in the transdermal patch drug delivery literature.

Skin Patch Example III

The amount of solids in #77 spray adhesive available from the 3M Company was determined by spraying 100 grams of the solution into a bottle and letting the solvents evaporate overnight. The solids weighed about 35 grams.

The solids consisted primarily of methyl methacrylate with tackifying and other additives.

A solution in methyl-ethyl-keytone and ethyl acetate was prepared of sprayed adhesive solids and lidocaine base in the ratio of 38% lidocaine base by weight and 62% solids of the #77 Spray Adhesive. A paintable fluid was formed by adding sufficient methyl-ethyl-ketone and ethyl acetate to dissolve the solids. The fluid was painted on a polyethylene film carrier sheet with a paintbrush, letting dry between coats by exposing it to heat at 85° F in a controlled oven.

After 3 coats the product was maintained in the oven at 85° for 24 hours to remove volatiles.

The resulting coating was very tacky, sufficient to adhere well to the skin. The adhesive layer was mounted on release paper in strips 2 inches wide. Patches of this product were applied to the flexor surface and extensor surface of the lower arm of the experimenter and the onset of anesthesia was observed.

This was done under 2 conditions, plain and with preapplication and wiping off of DMSO.

For the plain strip, onset time to establish total numbness of the skin under the patch was about two hours. By rubbing a small quantity of DMSO on the skin first, wiping it off, and applying the patch, the same degree of anesthesia was achieved in about one hour to one hour and a half, depending upon the area to which it was applied. The patch adhered well.

An enhancing effect similar to that of DMSO is obtainable with lauramide DEA-containing compounds, such as the Betadine® scrub of Examples I and II. The polyethylene film and the adhesive layer were removed from the skin very easily without adhesive remaining on the skin.

Skin Patch Example IV

A solution of lidocaine base 60% and polyvinyl chloride 40% by weight, was dissolved in tetrahydrofuran (THF) and cyclohexanone. This solution was painted on polyethylene film.

A light spray of 3M #77 Adhesive was applied as an intermediate layer to promote bonding to the polyethylene. Then three brush coats of this lidocaine base-PVC 60%, 40% in tetrahydrofuran and cyclohexanol were applied to the polyethylene and dried over a 24 hour period in the manner described in Example III.

This produced a clear non-tacky anesthetic plastic layer adhered to the film. When desired to make it adhere to the skin a light spray of #77 Spray Adhesive was applied and dried for 12 hours. This produced a tacky surface on the layer to which release paper was applied. When applied to the arm in the manner described for Example III, a good anesthetic block was achieved in about 2 to 2 1/2 hours. When DMSO was applied first and wiped off, a good to excellent block was achieved in 1 1/2 hours.

In this example the primary reservoir is the lidocaine-PVC layer. The adhesive serves to hold the reservoir layer

intimately to the skin and to transmit the drug from the reservoir layer to the skin.

Fluids, Creams and Lubricious Agents

It has also been found that polymers that display solubility in water and common solvents (for example polyethylene oxide (PEO) combined with a hydrophobic PVC powder in which anesthetic base is dissolved, provides a fluid system, cream or adhesive that can be applied to the skin in water base form, and in the presence of moisture retains its effectiveness. It can be removed with soap and water when desired. Water solubility permits application to hairy areas of the body for treatment of such painful processes as herpes zoster ("shingles") or post-herpes neuralgia.

A similar coating can be applied to a catheter or other medical device and when wetted provides a lubricious and topically anesthetizing surface.

Topical Application of Particles Example I

For topical fluid application, anesthetic plastic powders are first created. For this purpose a film is formed in an oven at 300°F employing a mixture of polyvinyl chloride 50% and lidocaine base 50%, by weight. The film is stretchy and tough. Combined with dry ice to embrittle it, the preformed film is passed through a grinder to produce a powder.

The powder is then suspended in water and applied to the skin as a watery suspension and covered with an occlusive dressing or a piece of moisture impermeable tape. A good block is established in 1 1/2 to 2 hours.

Application of Betadine pre-applied to the skin or used in the fluid to suspend the particles enhances the speed of onset.

Topical Application of Particles Example II

A powder is made of polyethylene oxide 33%, polyvinyl chloride 33% and lidocaine base 33%, by weight. A film of this

mixture is formed in an oven at 300°F and then ground with dry ice to produce a fine white powder. The powder is suspended in water and placed on the skin beneath an occlusive dressing. Anesthesia is established in about 1 1/2 to 2 hours. This powder has the advantage that the polyethylene oxide component is water soluble and sticky, so that it causes the suspension to stick better to the skin than does the powder of Example I. So long as it is kept covered and remains moist, anesthesia is prolonged. In this case the PEO acts as an adherent carrier for the lidocaine base, polyvinyl chloride particles.

Topical Application of Particles Example III

The cream of Example II was employed, except the water was replaced with Betadine scrub solution. The surgical scrub contains surfactants which speed the onset of block when this material is applied to the skin and covered with an occlusive dressing. Onset time for anesthesia was reduced from the time of Example II to about one hour.

Topical Application of Particles Example IV

An ointment was created using pulverized 50%-50% lidocaine base polyvinyl chloride film ground into a fine powder and suspended in Betadine surgical scrub. Onset of anesthesia was observed within 1 hour to 1 1/2 hours.

Endotracheal Tubes

Another area of interest that involves lidocaine-polyvinyl chloride plastics concerns endotracheal tubes. Several research centers have recently studied transmission of lidocaine across conventional endotracheal tube cuffs. Endotracheal tubes and cuffs formed by or coated with anesthetic plastic systems according to the present invention achieve superior results from the points of view of control and duration of anesthesia and ease of use.

Delivery of Other Drugs

Most of the specific examples just given have involved the base form of local anesthetic drugs of amide or ester type in PVC, methyl methacrylate, CPE, and EP carriers. Many other drugs with a benzene ring are relatively highly soluble or can be incorporated in PVC and other hydrophobic plastics. Similar to the base form of local anesthetics, these drugs are slowly released to the surface of the polymer. This provides an improved mechanism for formulating time-released medications for absorption e.g. from the gastro intestinal tract or by transdermal modalities as by transdermal patch, ear or nasal plugs or foam vaginal or rectal suppositories, etc. The plugs and suppositories in some instances comprise drug incorporated in plastic foam, as mentioned above, and in other instances comprise non-drug carrying compressible or deformable members that have an exterior, drug-containing plastic film, sheet or coating according to the invention as an outer covering.

The following examples of use illustrate broad further teachings of the invention in various fields of medicine and personal care.

ALLERGISTS

Prior to applying a pattern of allergens by needle to the skin, a topically anesthetizing, pressure-sensitive adhesive covering, according to the invention, is applied to the area. This preparatory step avoids pain of the needle. It may be applied at home before visiting the allergist. When used after administration of the allergens, it can reduce itching or pain.

In various instances the covering is a film, sheet or foam of anesthetizing hydrophobic plastic, which itself, or in conjunction with a pressure sensitive adhesive layer, contains a concentration of the anesthetic in solid solution or otherwise incorporated in the plastic. It produces prolonged dosage. See also: CONSUMER-NON PRESCRIPTION; DERMATOLOGY, below.

ANESTHESIOLOGY

A topically anesthetizing endotracheal tube and cuff enable the patient to tolerate the tube without choking or bucking while use of muscle relaxants to enable tolerance of the tube may be reduced or avoided. This leads to quicker recovery of body functions following a surgical procedure. The tube enables lower levels of general anesthesia to be maintained which can reduce anesthesia-related complications. Patient head movements associated with coughing or bucking, that can disrupt delicate operations such as eye or brain surgery, can be avoided.

Patient tolerance of the tube, produced by the long-acting local-anesthetizing effect, enables more intensive administration of breathing support in recovery and intensive care units by use of ventilator machines.

BALLOONS

See TUBES and CATHETERS; FILMS, SHEETS and FOAMS.

BURN DRESSINGS, BANDAGES AND COMPRESSES

Light weight, highly flexible anesthetizing plastic film, sheet, or foam coverings, bandages or applied coatings or creams according to the invention provide long-term comfort to burns, abrasions and incision sites. Conformability of the flexible coverings to large areas of the body enables intimate application and assures long-term integrity of the product. Dosage can be regulated by prescription of the concentration of anesthetic in the plastic due to the wide range of discovered solubility, and the ability to combine the drug with a similar non-therapeutic ingredient. The concentrations of drug in the product are unmistakably identified by color, such as red, yellow and green, in descending order of concentration of the anesthetic.

The films and foams may be applied without strong adhesives and may be painlessly removed.

Films or foams can be formed by application of emulsions that form the desired anesthetizing plastic covering. These can

be removed by washing when water or alcohol-soluble additives are employed.

Absorbent compresses are combined with an anesthetizing constituent. The constituent, as e.g. an array of screen-printed vinyl anesthetic spots or lines on a compress or bandage, or anesthetizing threads or fiber reservoirs, may be employed to controllably release topical anesthetic. Hydrophobic drug carrying fibers, deposits or other constituents are advantageously combined with absorptive threads or fibers to form a dual-purpose compress or bandage.

CARDIOLOGY

See ORAL MEDICATION-TIME RELEASE; TRANSDERMAL PATCHES; INSTRUMENTS AND DEVICES; TUBES AND CATHETERS.

CONSUMER NON-PRESCRIPTION PRODUCTS

A plastic strip bandage can apply its anesthetic at the absorptive compress or through the adhesive, as suggested at BURN DRESSINGS, BANDAGES AND COMPRESSES.

Thus attractive personal care products include: a spot-sized plastic strip, for sites of needle sticks as for taking blood or freezing of tissue; spot adhesive anesthetizers for insect bites; wide area anesthetizing plastic covering for skin exposed to poison ivy or poison oak or other itching conditions; a similar covering for burns; a scratch covering for the child, athlete, or adult; a painless bandage for use by infants and people with sensitive skin.

Other objects placed in a sensitive region inside or outside the body may be provided with an anesthetizing covering. Thus, a hot water bottle or an ice pack formed of PVC or having a PVC coating can administer topical anesthetic to a bruised or abraded area in conjunction with thermal therapy. Likewise anesthetizing foam cushions are achievable.

DENTISTRY

Rapid onset of topical anesthetic from foam and sheet via mucosal tissue of the mouth and gums can prepare the dental patient for a painful procedure or allay topical pain for extended periods following the procedure. An example is gum surgery. The controlled release properties due to selection of the plastic and concentration of the anesthetic produces sufficiently slow diffusion from the hydrophobic plastic to ensure that dosage is properly controlled and blood levels of lidocaine do not become excessive.

DERMATOLOGY

Anesthetic is released from films, sheets, foams, compresses, coatings and creams over selectable durations for patients with skin and neurological disorders. Patients with shingles or herpes infections or post herpes neuralgia and patients with hyper-sensitive and painful or itching skin conditions can thus be treated.

Patients can be prepared for minor skin surgery, dermabrasion, laser treatment, or electrolysis by pre-application to the site to be treated. Home application of a anesthetizing covering preceding the visit to the surgeon can reduce stay in the hospital or doctor's office. Likewise, customers desiring to have tatoos applied or removed may pre-apply an anesthetizing covering to avoid pain.

FILMS, SHEETS AND FOAMS

A thin film substrate of polyvinyl chloride that is highly flexible due to the presence of a large concentration (e.g. 50%) lidocaine base, can induce topical anesthesia to mucosal tissue very quickly and to the outer skin when in place an hour or so. More rapid onset of anesthesia of the skin can be achieved by use of benign penetration agents that are included in or applied to the anesthetizing film, sheet or foam.

A film, sheet or foam containing a selected mixture of anesthetic bases, itself, has a pressure sensitive adhesive character that can enhance transfer of the drug. Supplemental adhesive such as a thin layer of methacrylate based adhesive can be employed for added adhesion, with the layer serving as an intermediate transfer layer.

A highly flexible non-reservoir plastic film of less than 0.001 inch thickness such as polyethylene can support a thin, effective coating of reservoir polymer for short term use measured in hours or days.

Use of a water soluble film-forming polymer as a carrier of hydrophobic reservoir resin particles in which the drug is in solid solution provides a film with a water-activated adhesive surface, which, after use, can readily be washed away.

Depending upon the thickness of the film, sheet or foam, an anesthetic effect lasting for days, weeks, or longer can be achieved. To extend the period of effectiveness, it is only necessary to increase the thickness of the reservoir layer and/or the concentration of anesthetic base in solution in the polymer, or to control other parameters of the product such as choice of the drug, the plastic resin, and the character of the metering layer.

Anesthetizing plastic films or sheets may be "lay-flat", formed by casting or extrusion through a flat die. The blown film process as used in producing packaging film may be employed, in which the anesthetic base is provided in the compounded resin that is fed to the extruder that forms a hollow tube which is then expanded by a captured bubble of air. Application of a layer of the polymer-drug combination to various preformed films, sheets or other structures is also advantageous.

In other cases, the film is formed, as by free-form blowing of a tubular parison or blowing the parison in a mold, into a desired object, for instance into the form of an inflatable balloon to occlude a body passage, as the inflatable cuff of an

endotracheal tube, or the balloon of a Foley Catheter, or as a flexible obturator or probe.

In still other cases, the film is formed in situ as a coating on an object, as from solutions containing the resin and drug, from which a process solvent or carrier is evaporated.

Plastisols are likewise molded or cast to form films, sheets, foams, molded objects and coatings, and then are heated to congeal the resin as a permanent flexible structure or coating.

The density of foams that are formed depend, in the conventional way, upon the amount of blowing agent employed within the plastic-drug composition. An ear plug of plastic can administer drug via tissue in the ear, or a suppository can administer drug via rectal tissue. These may be of foam according to the invention or covered by a film or coating according to the invention.

GASTROENTEROLOGY

For naso-gastric and enteral feeding tubes, see TUBES AND CATHETERS.

INSTRUMENTS, DEVICES, and IMPLANTS

Endoscopes, ultra-sound catheter probes and other probes are provided with permanent anesthetizing plastic coverings or thin disposable, anesthetizing sheaths for anesthetizing mucosal or other tissue.

Implants, cushions and other devices that contact sensitive regions can likewise have permanent anesthetizing coverings or be encased in disposable sheaths.

Consumer products include ice packs, hot water bottles and cushions. These likewise have permanent, anesthetizing covers or thin, disposable anesthetizing sheaths.

Implanted anesthetizing strips, fibers or rods or injection of body-tolerable masses of polymer reservoir material carrying

the anesthetic can be introduced to painful sites such as to the site of cancer of the pancreas and exposed nerves in the posterior gutter along the spine.

NEUROLOGY

See: DERMATOLOGY; INSTRUMENTS, DEVICES and IMPLANTS; STRIPS, SUTURES, RODS, THREADS, FIBERS and NON-WOVENS.

ORAL MEDICATION-TIME RELEASE

Tiny solid polymer particles that serve as reservoirs are ingested in powder or tablet form, release the drug in a controlled manner as the particles pass through the gastro-intestinal tract and are excreted. In this manner drugs such as lidocaine or propathenone, administered systemically for anti-seizure or antiarrhythmic treatment, or for migraine headache, or drugs of similar structural properties, can be administered in a time-released manner in the gastric system. The drug is absorbed through the stomach and intestinal linings to progressively enter the blood stream.

ORTHOPEDICS and PROSTHETICS

Plastic cushioning for prosthetics, such as foam coverings for artificial limbs, provide anesthetizing stump contact surfaces that alleviate itching and discomfort for an extended time. The topical anesthetic contained in the polymer, in concentrations as high as 50% by weight, is released to the skin for extended periods. This system is particularly applicable to the new stump in its first fitting of a prosthetic. The inclusion of anesthetic in plastic cartilage replacements or in methacrylate bone cement for joint replacement is also feasible.

SURGERY

Shortened hospital stay, lower hospitalization cost, more rapid rehabilitation and reduction of persistent sensitivity following healing are all made possible by the novel products

that have been described. Topically anesthetizing drains, temporary anesthetizing implants and wound closings can significantly reduce pain of many surgeries. Examples are chest surgery, abdominal surgery and treatment of cancers.

See the Surgical scenario that was presented above, and: ANESTHESIOLOGY; BURN DRESSINGS, BANDAGES AND COMPRESSES; INSTRUMENTS, DEVICES AND IMPLANTS; ORTHOPEDICS AND PROSTHETICS; STRIPS, SUTURES, RODS, THREADS, FIBERS AND NON-WOVENS; AND TUBES and CATHETERS.

PODIATRY

Plasters and pads that produce prolonged relief from pain and discomfort of the feet have the construction of products described under CONSUMER NON-PRESCRIPTION; DERMATOLOGY.

The products are most effective upon areas of thin skin.

STRIPS, SUTURES, RODS, THREADS, FIBERS AND NON-WOVENS

Strips and sutures having an anesthetizing plastic exterior, formed of the reservoir polymer in which the anesthetic base is in solid solution, provide a local anesthetizing effect that decreases post-operative discomfort at the surgical site.

Conventional suture material, e.g. silk, polyester, glass or cotton suture materials have a plastisol coating applied, made of the reservoir polymer, with the drug in solid solution or otherwise incorporated. During manufacture, the plastisol is heated to congeal the polymer into a tenacious, anesthetizing suture covering.

In other cases, the sutures are monofilaments or composites that are themselves constituted of the reservoir polymer in which the drug is in solid solution or otherwise incorporated. Reinforcing fibers within the polymer render the suture inextensible.

Monofilaments may be extruded and drawn from a die, or a series of filaments may be twisted or otherwise formed into an extensible or nonextensible thread or yarn.

The fine constituent fibers of a non-woven fabric can likewise be formed by drawing of melted-anesthetic plastic from spinnerrettes followed by treatment to form the fibers into fabrics. Air laying, bonding or hydroentanglement are suitable non-woven-forming techniques for the anesthetic plastics, depending upon the choice of resin. The fibers in staple form may likewise be employed in a non-woven construction. An adhesive material used to bond fibers to form a non-woven fabric may also constitute a polymeric reservoir for the base form drug.

Rods of reservoir polymer may be formed by extrusion techniques, with the drug incorporated in the feed compound to the extruder, or may be formed by extrusion of a plastisol of reservoir resin and drug, followed by curing, or by casting. The rods may be highly flexible, for use within the body at places of flexing. They may have elastomeric properties, to permit stretching to conform to body movements. In other cases the rods may be nonextensible, e.g. fiber reinforced, to facilitate removal from the body by application of tension.

TRANSDERMAL PATCHES

Rugged transdermal skin patches employ large concentrations of selected drugs in solid solution in durable polymers. An example is lidocaine in base form in solid solution 50% by weight in polyvinyl chloride strips, or lidocaine, 30% by weight in methyl-methacrylate-based adhesive compositions.

A combination of a plastic strip reservoir, in which a high concentration of drug is in solid solution or otherwise incorporated, and an adhesive layer, also containing the drug, provides an effective system for attachment of the patch to a transfer region on the body, as behind the ear. In this example, the adhesive mass serves as the transfer layer, and is continuously resupplied by the solid plastic strip reservoir to achieve long term transdermal dosage.

In transdermal systems according to the techniques disclosed there is no need to be concerned about the protection of liquids

or delicate gels. Benefits include simpler packaging and storage, avoidance of need for precautions in user handling, and lowered cost.

One use for such a skin patch is for prolonged administration of propafenone or lidocaine for antiarrythmia or antiseizure medication or of lidocaine systemically for migraine headache. For the migraine application, the patch serves as a substitute for nasal spray administration of lidocaine that risks uncomfortable sensations if the sprayed lidocaine enters the throat from the nose.

TUBES AND CATHETERS

The exteriors of tubes and catheters are provided with an anesthetizing surface either in the form of a solvent-based coating or plastisol coating, or by having the structure of the tube or device fabricated of the polymer-anesthetic material, as by extruding or by casting of a plastisol.

Examples are, catheters, such as Foley catheters, urethral and ureteral catheters, endotracheal tubes, feeding tubes including naso-gastric and enteral feeding tubes, drains including Penrose drains, drainage stents, shunts, sheaths and reinforcing stents. The tubular devices themselves, or disposable sheaths for these devices, may be anesthetizing. Permanent lubricious coatings are provided on the exterior of catheters and other tubes, or lubricious coatings are applied at the time of use, that contain polymer-topical anesthetic constituents for numbing the contacted mucosal tissue during insertion and manipulation of the catheter.

UROLOGY

The tubes and balloons of Foley catheters are provided with a covering, or the balloon wall is formed solidly from the anesthetic plastic system. Likewise, urethral and ureteral catheters, stents and shunts can be formed or coated. All can have a unique anesthetizing effect that promotes comfortable

tolerance. The tubes and catheters may be provided with an anesthetizing lubricious coating.

For more rapid onset, an initial water-soluble form of the anesthetic, such as lidocaine hydrochloride may be presented at the outer surface of any of these devices for achieving rapid anesthesia during initial introduction.

VETERINARY

The veterinary applications correspond to the medical applications that have been described. Pets and other animals will be less likely to disturb wound dressings, bandages, casts and transdermal patches that incorporate anesthetizing plastic.

What is claimed is:

1. Each of the products and compositions disclosed in the above description and similar products and compositions, comprised of drug delivery polymer, or anesthetizing polymer as described, in which the drug or anesthetic component has an aromatic ring, the polymer is hydrophobic, and the concentration of the drug in the polymer is at least 5%, preferably in excess of 10%, preferably, in the case of anesthetics, in excess of 20% and preferably in the case of lidocaine incorporated in PVC, in excess of 30%.

2. The methods of fabrication disclosed in the above description and the general method of dissolving or otherwise incorporating the anesthetics and drugs in conventional polymer to form the products of claim 1.

3. The product of claim 1 in which the anesthetic or drug is more soluble in the polymer than in water.

4. The product of claim 1 in which the drug or anesthetic incorporates at least one free amide or amine hydrogen in its structure.

5. The product of claim 1 wherein the drug or anesthetic has the structure

$$Bz - Z - (CH_2)_n - NR^1 R^2$$

where:

Bz is a substituted or unsubstituted benzene ring;
Z is an ester or amide linkage;
and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and N is an integer.

6. The product or composition of claim 1 comprising a topical anesthetic compound which is more soluble in the polymer than in the water, the anesthetic compound being substantially

dissolved in the polymer, the amount of the anesthetic base dissolved or otherwise incorporated in the polymer rendering the composition suitable as a topical anesthetic agent.

7. A composition comprising an anesthetic base dissolved or otherwise incorporated in a hydrophobic polymer.

8. The composition of claim 7 comprising a prolonged drug release system.

9. The composition of claim 7 in which the anesthetic base has the form

$$Bz - Z - (CH_2)_n - NR^1 R^2$$

where:

Bz is a substituted or unsubstituted benzene ring;
Z is an ester or amide linkage;
and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and N is an integer.

10. The composition of claim 8 in which the anesthetic base is selected from the class consisting procaine, mepivacaine, lidocaine, chloroprocaine, tetracaine, etidocaine, prilocaine, etidocaine, replivicaine, diphenhydramine and benzocaine.

11. The system of claim 7 in which the anesthetic is more soluble in the polymer than in water.

12. The composition of claim 7 wherein the anesthetic base is lidocaine.

13. The composition of claim 7 wherein the anesthetic base is propafenone.

14. The composition of claim 12 or 13 wherein the amount of said anesthetic base dissolved or otherwise incorporated in the polymer is suitable for use as an antiarrhythmia or antiseizure agent.

15. The composition of claim 7 wherein the composition is in the form of orally administrable, indigestible granules.

16. The composition of claim 7 or 12 wherein the amount of said anesthetic base dissolved or otherwise incorporated in the polymer is suitable for use as a topical anesthetic for mucosal or other tissue within the body.

17. The composition of claim 7 or 12 wherein the amount of said anesthetic base dissolved or otherwise incorporated in the polymer is suitable for use as a topical anesthetic on the skin.

18. A product comprising the composition of claim 16 or 17 in the form of a shaped, heat-cured plastisol.

19. A product comprising the composition of claim 16 or 17 in the form of a foam.

20. A product comprising the composition of claim 16 or 17 in the form of a sheet, film, tape or a coating or layer upon a substrate.

21. A product comprising the composition of claim 16 or 17 in the form of a suture or fiber.

22. A product comprising the composition of claim 16 or 17 shaped for insertion in a passage of the body.

23. The product of claim 19, 20, 21 or 22 including a reinforcing fiber.

24. The product of claim 19, 20, 21 or 22 in which the foam, sheet, film, tape, coating or layer upon a substrate, suture or fiber includes an adhesive layer capable of conducting the anesthetic to tissue to which the adhesive is adhered.

25. The product of claim 19, 20, 21, 22, 23 or 24 in the form of a heat-cured plastisol.

26. The product of claim 19, 20, 21, 22 or 23 in the form of a deposited or printed layer.

27. The composition of claim 7 wherein said polymer is selected from the group consisting of polyvinyl halides, halogenated polyolefins, cellulosic resins, polystyrenes, polyvinyl butyral resins, alkyl alkylacrylate resins, alkyl acrylate resins, acrylonitrile rubbers, halogenated rubbers, polyester resins, polyformaldehyde resins and combinations thereof.

28. The composition of claim 7 wherein said polymer is a polyvinyl halide.

29. The composition of claim 28 wherein said polymer comprises plasticized polyvinyl chloride.

30. The composition of claim 28 wherein said polymer is unplasticized polyvinyl chloride.

31. The composition of claim 7 in which the anesthetic is a local or topical anesthetic, or an antiarrhythmia or antiseizure agent.

32. A composition comprising an anesthetic base dissolved or otherwise incorporated in a polymer in an amount suitable for use as an antiarrhythmia or antiseizure agent.

33. The composition of claim 32 in which the anesthetic is lidocaine.

34. The composition of claim 32 in which the anesthetic is propafenone.

35. A composition comprising a drug having at least one aromatic ring, the drug being in base form and incorporated in thermoplastic resin.

36. The composition of claim 35 wherein said thermoplastic resin has a processing temperature between about 250° and 450°F.

37. The composition of claim 35 wherein said drug is present below the surface of said resin in a diffusible state enabling it to diffuse to the surface of the resin for release.

38. The composition of claim 35 wherein the drug is selected from the group consisting of anesthetics, local anesthetics and topical anesthetics.

39. The composition of claim 35 wherein the drug is selected from the group consisting of antiarrhythmia drugs; antiseizure drugs; adrenergic blocking drugs; sympathomimetic drugs; analgesics or antipyretics and stimulants of the nervous system.

40. The composition of claim 34 wherein said polymer is selected from the group consisting of polyvinyl halides, halogenated polyolefins, cellulosic resins, polystyrenes, polyvinyl butyral resins, alkyl alkylacrylate resins, acrylonitrile rubbers, halogenated rubbers, polyester resins, polyformaldehyde resins and combinations thereof.

41. The composition of claim 7 or 35 configured to lie adjacent a surgical or trauma site to administer anesthetic or other medication to the site, or configured as a flexible wall or fiber to be exposed to contact tissue; or is configured to deliver local or topical anesthetic in the region of an incision or wound; or is configured as a form object to engage tissue; or is a plug or suppository for insertion in the ear, nose, mouth, vagina, or rectum; or is configured to perform an added function such as that of a fluid-conducting tube such as a feeding tube, drainage tube,an irrigation tube or fluid drug administration tube.

42. The composition of claim 35 wherein a plurality of drugs are incorporated in the resin, wherein the plurality including drugs that have the same or different properties.

43. The composition of claim 35 in which the drug is a plasticizer for the resin.

44. The composition of claim 43 including a non-therapeutic plasticizer incorporated in the resin.

45. The composition of claim 44 in which the proportion of the two plasticizers is selected to assist in achieving a predetermined desired rate of release of the drug.

46. A wound or incision-treatment device configured to reside at a surgical site, and formed at least in part of thermoplastic resin in which at least a topical anesthetic or other drug is dissolved or otherwise incorporated, the topical anesthetic or other drug having at least one aromatic ring.

47. A wound or incision-treatment device according to claim 46 wherein the device is a tube having a surface exposed to contact tissue to be treated, or is a film having a surface exposed to contact tissue to be treated, or is a compress or bandage, or is formed at least in part of one or more

thermoplastic fibers in which the drug is present; or is a suture formed at least in part of thermoplastic resin in which the drug is dissolved or otherwise incorporated, or comprises fibers that are at least part of a textile material such as a non-woven material or comprises fibers that are hydrophobic or in which hydrophobic fibers are combined with hydrophilic fibers capable of containing an aqueous substance that promotes release and transport of the drug from the hydrophobic resin, or combined with a fluid, ointment or adhesive that promotes transport of the drug from the resin; on in which the fluid, ointment or adhesive contains a drug, and the drug from the resin is effective to replenish the drug in the fluid, ointment or adhesive; or is the drug dissolved or otherwise incorporated in the resin includes topical anesthetic, or in which fluid, ointment or adhesive includes surfactant that promotes diffusion of the drug through tissue, or in which the fluid, ointment or adhesive that cooperates with the drug dissolved or otherwise incorporated in the resin includes a combination of topical anesthetics and an emulsifier such as a fatty acid ester.

48. A wound or incision-treatment device comprising fibers or a deposit of a composition comprising hydrophobic resin in which a drug having an aromatic ring is dissolved or incorporated.

49. The wound or incision-treatment device according to claim 43 including hydrophilic fibers.

50. The device of claim 48 or 49 comprising a moisture absorbing compress that includes the composition.

51. The device of claim 50 comprising a printed deposit of the composition.

52. A composition comprising propafenone in effective quantities disposed in a thermoplastic resin.

53. The composition of claim 52 wherein said propafenone is in base form dissolved or otherwise incorporated in said resin and is adapted for exposure to the body under conditions in which propafenone released from the resin is gradually released to enter the bloodstream.

54. The process of forming a drug delivery composition comprising selecting a hydrophobic polymer in which a drug, in base form, having an aromatic ring is soluble or otherwise can be incorporated, and manipulating the resin and drug, to cause the drug to be incorporated in the resin.

55. The method of claim 54 comprising forming a plastisol that includes the resin and coating or configuring the plastisol, and subsequently heating the plastisol to congeal it.

56. The method of claim 55 including forming the plastisol.

57. The method of claim 55 including applying the plastisol to a substrate prior to heating it.

58. The method of forming a drug delivery composition comprising incorporating a drug having an aromatic ring and a molecular structure similar to a resin plasticizer into a resin in which said plasticizer can be incorporated.

59. The method of claim 58 wherein said drug is dissolved into a resin in which a phthalate ester is soluble.

60. The method of claim 54 in which the polymer is selected from the group consisting of polyvinyl halides, halogenated polyolefins, cellulosic resins, polystyrenes, polyvinyl butyral resins, alkyl alkylacrylate resins, acrylonitrile rubbers, halogenated rubbers polyester resins, polyformaldehyde resins and combinations thereof.

61. A method of claim 54 comprising forming a drug delivery composition in the form of orally administratable granules of fine or coarse powders, comprising forming an extrusion of the resin in which the base form of drug having a aromatic ring is dissolved or otherwise incorporated and then grinding the extrusion to form the granules.

62. A drug composition, or an intermediary composition used in forming a drug composition, comprising a drug in base form, selected from the group having an aromatic ring and consisting of propathenone, lidocaine, dibucaine, prolicane, atenol, pseudoephedrine, terbutaline, phenylpropanolamine, acetaminophen, ibuprofen, phenacetin and methylphenidate said drug dissolved or otherwise incorporated in a thermoplastic resin.

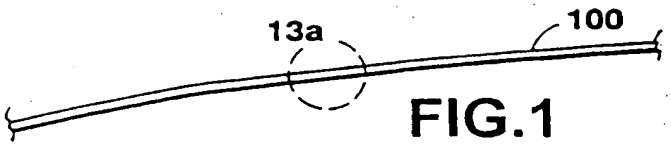

FIG.1

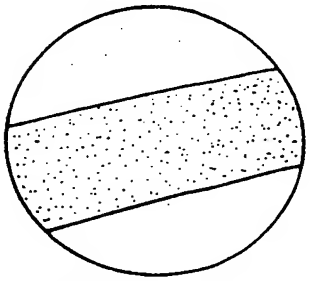

FIG. 1a

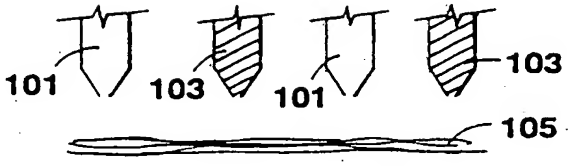

FIG. 4

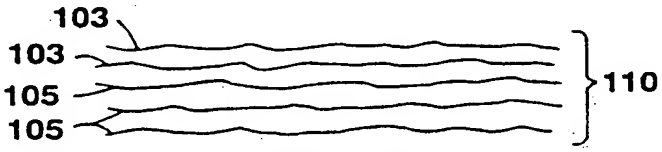

FIG. 5

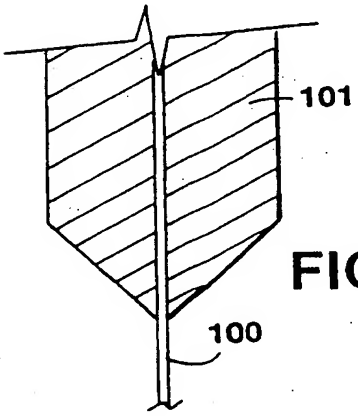

FIG. 2

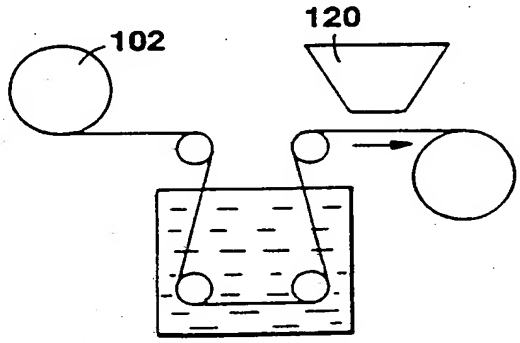

FIG. 6

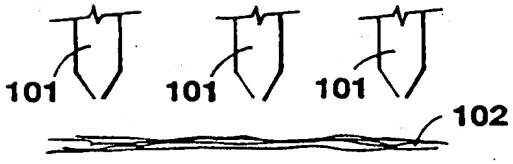

FIG. 3

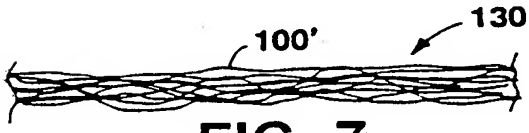

FIG. 7

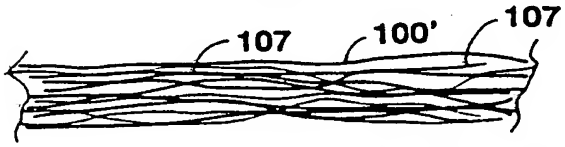

FIG. 8

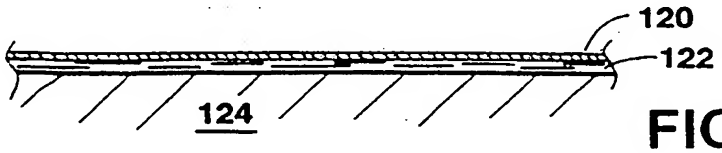

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04948

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61M 5/32, 25/00
US CL :601/48; 604/265; 623/11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 602/48, 52, 54; 604/112, 113, 265, 266; 623/11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

MERCK INDEX

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, APS
Search Terms: anesthetic, base, polymer, medical, lidocaine, propafenone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,279,594 A (JACKSON) 18 January 1994, entire reference.	1-12, 14-17, 20, 22, 26-33, 35, 36, 38, 39, 41-44, 46, 49, 53-57 --- 13, 18, 19, 21, 23-25, 31, 32, 34, 37, 40, 45, 47, 48, 50-52
Y	US 4,898,591 A (JANG et al) 06 February 1990, note the reinforcement fibers within the polymeric catheter.	23

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 JUNE 1997	Date of mailing of the international search report 18 JUL 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHALIN SMITH Telephone No. (703) 308-2988

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04948

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,978,203 A (WISE) 31 August 1976, note the pharmaceutically active suture.	21
Y	US 4,612,337 A (FOX, JR. et al) 16 September 1986, note the methods of making pharmaceutically active sutures and the like.	23
X --- Y	US 5,417,671 A (JACKSON) 23 May 1995, entire reference.	1-12, 14-17, 20, 22, 26-30, 33, 35-44, 46, 49, 53-57 --- 13, 18-19, 21, 23-25, 31, 32, 34, 45, 47, 48, 50-52
Y	US 3,577,516 A (GOULD et al) 04 May 1971, note the plastisol spray bandage.	18, 19, 25, 50-52
Y	US 5,330,452 A (ZOOK) 19 July 1994, note the adhesive bandage with topically effective anesthetic therein as well as foam and gel formation.	1-57
Y	US 5,478,567 A (NAKAGAWA et al) 26 December 1995, note the adhesive analgesic polymeric bandage as well as plasticizers, foams and the like therein.	1-57